



Metabolic Syndrome, Prediabetes, and Brain Abnormalities on MRI in Patients With Manifest Arterial Disease: The SMART-MR Study

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Audrey M. Tiehuis,¹ Yolanda van der Graaf,¹
Willem P.T.M. Mali,¹ Koen Vincken,¹
Majon Muller,² and Mirjam I. Geerlings,¹
for the SMART Study Group

OBJECTIVE

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors leading to atherosclerosis and diabetes. Diabetes is associated with both structural and functional abnormalities of the brain. MetS, even before diabetes is diagnosed, may also predispose to cerebral changes, probably through shared mechanisms. We examined the association of MetS with cerebral changes in patients with manifest arterial disease.

RESEARCH DESIGN AND METHODS

Cross-sectional data on MetS and brain MRI were available in 1,232 participants with manifest arterial disease (age 58.6 ± 10.1 years; 37% MetS). Volumes of brain tissue, ventricles, and white matter hyperintensities (WMH) were obtained by automated segmentation and expressed relative to intracranial volume. Infarcts were distinguished into lacunar and nonlacunar infarcts.

RESULTS

The presence of MetS ($n = 451$) was associated with smaller brain tissue volume (B -0.72% [95% CI $-0.97, -0.47$]), even in the subgroup of patients without diabetes (B -0.42% [95% CI $-0.71, -0.13$]). MetS was not associated with an increased occurrence of WMH or cerebral infarcts. Impaired glucose metabolism, abdominal obesity, and elevated triglycerides were individual components associated with smaller brain volume. Obesity and hypertriglyceridemia remained associated with smaller brain volume when patients with diabetes were excluded. Hypertension was associated with an increased occurrence of WMH and infarcts.

CONCLUSIONS

In patients with manifest arterial disease, presence of MetS is associated with smaller brain volume, even in patients without diabetes. Screening for MetS and treatment of its individual components, in particular, hyperglycemia, hypertriglyceridemia, and obesity, may prevent progression of cognitive aging in patients with MetS, even in a prediabetic stage.

It is increasingly recognized that both the metabolic syndrome (MetS) and diabetes are associated with accelerated cognitive decline in older individuals (1–3). Brain imaging studies in patients with diabetes report an increased occurrence of brain atrophy and vascular lesions (white matter hyperintensities [WMH] and lacunar infarcts [LIs]) (4). However, there is limited current literature about the relation

¹University Medical Center Utrecht, Utrecht, the Netherlands

²Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands

Corresponding author: Mirjam I. Geerlings, m.geerlings@umcutrecht.nl.

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between MetS and structural brain changes on MRI (5–13). Previous cross-sectional studies showed no differences in brain volume between subjects with and without MetS (5,6), but high HbA_{1c} has been identified as a risk factor for a greater rate of brain atrophy over 6 years in a prospective study (7). For the relation of MetS with ischemic stroke, contradictory results have been reported (8–12), as well as for the relation of MetS with WMH (5,13). Not all of these studies used volumetric assessment of WMH and measures of brain atrophy.

The underlying pathway for accelerated cognitive aging in MetS is unclear. MetS and diabetes are likely to affect the brain through shared mechanisms. These mechanisms involve atherosclerotic disease (14), but direct effects of disturbed insulin and glucose homeostasis on the brain may also play a role (15). There may also be differences between MetS and diabetes-induced cerebral damage. Some features that are part of MetS such as disturbances in lipid metabolism and generalized inflammation (16,17) may be less pronounced in patients with diabetes without MetS.

MetS is present in nearly 20–25% of apparently healthy individuals and in 35–45% of patients with clinical manifestations of atherosclerosis (18,19). Patients with atherosclerotic disease and MetS may have a higher risk of brain damage than patients with atherosclerotic disease without MetS, even in individuals without established diabetes (10).

The current study investigated the association between MetS, brain volumes, and cerebrovascular lesions on MRI in patients with manifest arterial disease. In this large patient cohort with wide age range, in which MetS is highly present, we used quantitative volumetric measurements and also examined the relation of the individual components of MetS to brain MRI findings.

RESEARCH DESIGN AND METHODS

Second Manifestations of Arterial Disease Magnetic Resonance Study

The current study is a cross-sectional study within the Second Manifestations of ARterial Disease (SMART) Magnetic Resonance (MR) study, a prospective cohort study within the SMART study (18),

to investigate causes and consequences of brain changes on MRI in patients with atherosclerotic disease. In the SMART study, all eligible patients, newly referred to the University Medical Center Utrecht with symptomatic atherosclerotic disease or risk factors for atherosclerosis, were screened for additional risk factors and severity of atherosclerosis. The baseline examination was performed during a 1-day visit to our medical center. Between May 2001 and December 2005, an MR investigation of the brain was added to the baseline examination as part of the SMART-MR study. Patients were eligible for MRI of the brain if they were included with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm (AAA) and if they had no MR contraindications. Coronary artery disease was defined as myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty in the past or at inclusion. Patients with a transient ischemic attack or stroke at inclusion and patients who reported stroke in the past were considered to have cerebrovascular disease. Peripheral arterial disease was defined as surgery or angioplasty of the arteries supplying the lower extremities in history, intermittent claudication, or rest pain at inclusion. AAA was defined as present AAA (distal aortic diameter ≥ 3 cm) or previous AAA surgery. The SMART study and SMART-MR study were approved by the ethics committee of our institution, and written informed consent was obtained from all participants.

MRI Protocol and Brain Segmentation

The MR investigations were performed on a 1.5-T whole body system (Gyrosan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time [TR]/echo time [TE], 235/2 ms), T2-weighted turbo spin-echo sequence (TR/TE, 2,200/11 and 2,200/100 ms), T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time [TI], 6,000/100/2,000 ms), and an inversion recovery sequence (TR/TE/TI, 2,900/22/410 ms; field of view, 230 \times 230 mm; matrix size, 180 \times 256; slice thickness, 4.0 mm; no gap, 38 slices).

We used the T1-weighted gradient-echo, inversion recovery, and FLAIR

sequences for brain segmentation (20). The segmentation program distinguishes cortical gray matter, white matter, sulcal, ventricular cerebrospinal fluid, and WMH. The segmentation analysis was visually checked for the presence of infarcts and adapted if necessary. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, WMH volume and infarcts. All volumes cranial to the foramen magnum were included. Thus the total brain volume includes cerebrum, brainstem, and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and volumes of the sulcal and ventricular cerebrospinal fluid.

Brain Atrophy

Total brain volume was expressed relative to ICV as the brain parenchymal fraction (BPF), an indicator for global brain atrophy, which represents the percentage of the ICV that is occupied by brain tissue. Ventricular enlargement, an indicator of subcortical brain atrophy, was also expressed relative to ICV as the ventricular fraction (VF).

Infarcts and WMH

Infarcts were rated by two trained investigators and a neuroradiologist, blinded to clinical information, and reevaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images to distinguish them from WMH. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and absence of gliosis. Brain infarcts were categorized as cortical infarcts, LIs, large subcortical infarcts, and infratentorial infarcts. We defined LIs as infarcts 3–15 mm in diameter located in the subcortical white matter, thalamus, or basal ganglia. Silent lacunes were defined as LIs in patients with no history of cerebrovascular disease. Large subcortical infarcts were sized >15 mm and were not confluent with cortical infarcts. Infratentorial infarcts were located in the brainstem or cerebellum. Volumes of total WMH were expressed relative to ICV (percentage).

Vascular Risk Factors

During the patient's visit at the medical center, an overnight fasting venous blood

sample was taken to determine glucose and lipid levels. Height and weight were measured without shoes and heavy clothing, and BMI was calculated (kg/m^2). Blood pressure (mmHg) was measured twice with a sphygmomanometer, and the average of the two measures was calculated. Smoking habits and alcohol intake were assessed with questionnaires. Pack years of smoking were calculated, and alcohol intake was never, former, or current. Patients who had quit drinking during the past year were assigned to the category current alcohol intake. Ultrasonography was performed to measure the intima-media thickness (IMT; mm) in the left and right common carotid arteries, represented by the mean value of six measurements. IMT is a marker for the extent of subclinical atherosclerosis and a surrogate measure for the burden of generalized atherosclerosis.

Definition of MetS and Diabetes

MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria (21). Three or more of the following metabolic abnormalities were required: impaired glucose metabolism (>6.1 mmol/L and/or use of glucose-lowering agents), elevated blood pressure (>130 mmHg systolic and/or >85 mmHg diastolic and/or use of blood pressure-lowering agents), low HDL cholesterol (<1.04 mmol/L in men and <1.29 mmol/L in women), elevated triglycerides (>1.70 mmol/L), or abdominal obesity (waist circumference >102 cm in men and >88 cm in women).

Diabetes was defined as a known history of diabetes, a fasting glucose level of ≥ 7.0 mmol/L, or self-reported use of oral antidiabetes drugs or insulin.

Data Analysis

Of the 1,309 patients included in the SMART-MR study, 77 patients were excluded from the analyses because of irretrievable MR data ($n = 19$), missing FLAIR images ($n = 14$), or artifacts ($n = 44$). Thus the analytical sample consisted of 1,232 patients. The cross-sectional association of MetS and its individual (dichotomous) components with brain volumes and WMH was assessed with linear regression analysis (expressed with regression coefficients B), and the association with brain infarcts was assessed with logistic regression models (expressed as odds ratio [OR]). We used multiple imputation (10

data sets) using the statistical program R (aregImpute version 2.10.0) to address missing values in the study sample of 1,232 patients. Data were analyzed using SPSS version 20 (Chicago, IL) by pooling the 10 imputed data sets. The variables with the highest percentage of missing values were impaired glucose metabolism (5.5%), elevated blood pressure (3%), waist (4.3%), and alcohol and smoking (both 8.1%). The other variables all had 2% or less missing.

These analyses were adjusted for age and sex (model 1) and additionally for other potential confounders (alcohol use, smoking, IMT, and history of cerebrovascular disease; model 2).

WMH volumes (percentage ICV) were log transformed (\ln) to normalize the distribution and entered in the model as a continuous variable. Regression coefficients B or OR with 95% CI were given for all results.

RESULTS

Baseline characteristics of 1,232 patients are given in Table 1. The mean age of the cohort was 58.6 ± 10.1 years, and there was a male predominance (79%), which was adjusted for in the multivariate analyses. The criteria for MetS were met by 451 (36.6%) patients.

Patients with MetS had more pronounced global brain atrophy: the BPF in the patients with MetS was 78.4 ± 3.0 versus $79.3 \pm 2.7\%$ in the patients without MetS (B -0.72% [95% CI $-0.97, -0.47$]; model 1) (Table 2). Additional adjustment for alcohol use, smoking, history of cerebrovascular disease, and IMT only mildly attenuated the regression coefficient B (-0.67% BPF [95% CI $-0.91, -0.42$]; model 2). Furthermore, exclusion of patients with a brain infarct on MRI (LI and/or non-LI; $n = 348$) did not materially change these results (B -0.65% [95% CI $-0.93, -0.38$]).

In the subgroup of patients with symptomatic arterial disease without diabetes, MetS was also significantly related to BPF, although less strongly (B -0.44% [95% CI $-0.7, -0.1$]) (Table 3).

The degree of ventricular enlargement (subcortical brain atrophy) was not different in patients with and without MetS (VF, B 0.08% [95% CI $-0.02, 0.18$]).

Patients with MetS did not have more WMH or cerebral infarcts than patients without MetS (WMH, B 0.04 [95% CI

$-0.07, 0.16$]; LIs, OR 1.03 [95% CI $0.76, 1.39$]; non-LIs, OR 1.27 [95% CI $0.94, 1.72$]).

When individual components were studied, the presence of impaired glucose metabolism, abdominal obesity, and elevated triglycerides was significantly associated with global brain atrophy (impaired glucose metabolism, -0.70% decrease in BPF [95% CI $-0.95, -0.45$]; abdominal obesity, -0.45% decrease in BPF [95% CI $-0.72, -0.19$]; elevated triglycerides, -0.37% decrease in BPF [95% CI $-0.62, -0.12$]) (Table 2). The strength of the association of obesity and elevated triglycerides with BPF decreased mildly after exclusion of patients with diabetes (Table 3). Elevated blood pressure was associated with LIs and non-LIs (Table 2) and borderline significantly with increased WMH volume.

CONCLUSIONS

In this cohort of 1,232 patients with manifest arterial disease, the presence of MetS is associated with more global brain atrophy. MetS was not independently associated with an increased occurrence of WMH or cerebral infarcts.

Brain atrophy (characterized by widening of the sulci, narrowing of the gyri, and enlargement of the ventricles) is a common finding on brain MRI in older people (22). In one of our previous cross-sectional analyses in the SMART-MR cohort, total brain volume decreased with a mean of 0.18% per year older (23). Other recent studies report mean decreases of 0.21 – 0.23% total brain volume per year older (24,25). At old age (average age 73 and 80 years), decreases of 0.31% and 0.30% total brain volume per year, respectively, were found (26,27). This suggests that MetS induces brain changes comparable to accelerated aging. This is of clinical importance as the extent and rate of progression of global brain atrophy have been related to cognitive deterioration and conversion to dementia (28,29).

Evidence from prospective studies show that the clustering of risk factors in MetS is associated with cognitive decline (1,30). Less is known about the relation between MetS and cerebral changes on MRI. Two previous cross-sectional studies showed no significant differences in brain volume on MRI between subjects with and without MetS. One was performed in 819 community-dwelling

Table 1—Characteristics of the participants (n = 1,232)

	MetS (n = 451)	No MetS (n = 781)	P value
Demographic factors			
Age, years	59.1 (9.7)	58.3 (10.4)	0.15
Sex, male	78%	80%	0.32
MetS criteria			
Number of criteria present	3 (3–4)	1 (1–2)	0.00
Impaired glucose metabolism	72%	21%	0.00
Elevated blood pressure	94%	76%	0.00
Low HDL cholesterol	60%	14%	0.00
Elevated triglycerides	74%	18%	0.00
Abdominal obesity	63%	12%	0.00
Diabetes	41%	10%	0.00
Measurements			
Fasting glucose, mmol/L	7.2 (2.4)	5.7 (1.1)	0.00
Glucose-lowering medication or insulin	22%	6%	0.00
Systolic blood pressure, mmHg	145 (21)	140 (21)	0.52
Diastolic blood pressure, mmHg	83 (11)	82 (11)	0.56
Antihypertensive medication	79%	69%	0.00
Cholesterol, mmol/L	5.1 (1.1)	4.9 (1.0)	0.60
HDL cholesterol, mmol/L	1.1 (0.3)	1.4 (0.4)	0.00
Triglycerides, mmol/L	2.3 (1.3)	1.4 (0.9)	0.00
Lipid-lowering medication	67%	67%	1.00
Waist, cm	101.9 (10.0)	91.7 (9.7)	0.39
BMI, kg/m ²	28.9 (3.9)	25.5 (3.0)	0.00
IMT, mm	0.99 (0.34)	0.92 (0.29)	0.07
Comorbid risk factors			
Current alcohol consumption	68%	79%	0.00
Smoking	38%	35%	0.24
Cerebrovascular disease	23%	23%	0.90
Coronary artery disease	59%	59%	0.97
Peripheral artery disease	27%	19%	0.00
AAA	11%	7%	0.05

Data shown are mean (SD), median (interquartile range), or proportions (in percentages). Diabetes is known type 2 diabetes and/or fasting glucose ≥ 7.0 mmol/L.

subjects using fully automated structural image evaluation (SIENAX) (5). The other (6) was performed in 1,812 middle-aged persons using a semiquantitative 10-point scale. High HbA_{1c} was identified as a risk factor for a greater rate of brain atrophy

(assessed by SIENA) over 6 years in a prospective study (7) among 201 normal individuals, suggesting a link between MetS and late-life brain tissue loss. MetS has been reported to be a risk factor for ischemic stroke and silent

brain infarction in studies among healthy people and in patients with coronary heart disease (8–11), but in 2,197 Chinese patients with type 2 diabetes without cerebrovascular disease at baseline, MetS failed to predict ischemic stroke and in contrast, macrovascular disease (ischemic heart disease and middle cerebral artery stenosis), and microvascular disease (retinopathy) contributed to the occurrence of incident stroke independently (12). No association between MetS and WMH was found in middle-aged people (n = 1,812) in whom relatively crude visual rating methods were applied (6), but in another study among 1,030 healthy subjects using the same rating scale, MetS was associated with every grade of leukoaraiosis (13).

We showed that the relation between MetS and global brain atrophy attenuated but remained statistically significant in our cohort after exclusion of known patients with diabetes and patients with a fasting glucose level ≥ 7.0 mmol/L. The progression from normal glucose metabolism through impaired glucose tolerance to diabetes is thought to be a gradual progress in which insulin resistance plays a crucial role. Our results therefore suggest that cerebral changes may already develop in a pre-diabetic stage.

The clustered cardiovascular factors in MetS, like in type 2 diabetes, may mediate their effect on the brain through a common pathway, most likely cardiovascular disease. However, vascular disease is unlikely to be the sole determinant. For example, studies in type 2 diabetes have shown that statistical

Table 2—Association between MetS and brain MRI in participants with symptomatic arterial disease (n = 1,232)

	Global brain atrophy (BPF, %) B (95% CI)	Subcortical brain atrophy (VF, %) B (95% CI)	In WMH (%) B (95% CI)	LIs (n = 232) OR (95% CI)	Non-LIs (n = 216) OR (95% CI)
MetS					
Model 1	−0.72 (−0.97, −0.47)*	0.08 (−0.02, 0.18)	0.04 (−0.07, 0.16)	1.03 (0.76, 1.39)	1.27 (0.94, 1.72)
Model 2	−0.67 (−0.91, −0.42)*	0.07 (−0.03, 0.17)	0.01 (−0.10, 0.13)	0.98 (0.70, 1.37)	1.33 (0.94, 1.90)
Individual components^a					
Impaired glucose metabolism	−0.70 (−0.95, −0.45)*	0.09 (−0.01, 0.20)	0.05 (−0.07, 0.17)	0.95 (0.70, 1.28)	1.05 (0.77, 1.44)
Elevated blood pressure	−0.29 (−0.61, 0.04)	0.11 (−0.02, 0.24)	0.13 (−0.02, 0.27)	2.37 (1.43, 3.92)*	2.30 (1.40, 3.78)*
Low HDL cholesterol	−0.18 (−0.44, 0.08)	−0.03 (−0.13, 0.08)	0.08 (−0.04, 0.20)	0.72 (0.52, 1.01)	0.88 (0.63, 1.22)
Elevated triglycerides	−0.37 (−0.62, −0.12)*	0.02 (−0.08, 0.12)	−0.03 (−0.15, 0.09)	1.01 (0.74, 1.38)	1.20 (0.88, 1.63)
Abdominal obesity	−0.45 (−0.72, −0.19)*	0.06 (−0.05, 0.16)	0.02 (−0.11, 0.14)	1.09 (0.79, 1.51)	1.28 (0.93, 1.75)

Non-LIs include cortical, large subcortical, or infratentorial infarcts. Model 1 is adjusted for age and sex. Model 2 is as model 1 but additionally adjusted for current smoking and alcohol intake, IMT, and history of cerebrovascular disease. ^aAdjusted for age and sex. *P < 0.01.

Table 3—Association between MetS and brain MRI in participants with symptomatic arterial disease without diabetes (n = 975)

	Global brain atrophy (BPF, %) B (95% CI)	Subcortical brain atrophy (VF, %) B (95% CI)	In WMH (%) B (95% CI)	LIs (n = 162) OR (95% CI)	Non-LIs (n = 156) OR (95% CI)
MetS					
Model 1	−0.4 (−0.7, −0.1)†	0.05 (−0.07, 0.17)	−0.01 (−0.15, 0.13)	0.79 (0.53, 1.18)	1.38 (0.95, 2.00)
Model 2	−0.42 (−0.70, −0.13)†	0.04 (−0.08, 0.15)	−0.03 (−0.17, 0.11)	0.71 (0.46, 1.10)	1.48 (0.96, 2.27)
Individual components^a					
Impaired glucose metabolism ^b	−0.27 (−0.59, 0.05)	0.002 (−0.13, 0.13)	−0.06 (−0.21, 0.09)	0.57 (0.36, 0.91)*	0.85 (0.55, 1.31)
Elevated blood pressure	−0.20 (−0.54, 0.14)	0.09 (−0.05, 0.23)	0.10 (−0.05, 0.26)	3.00 (1.62, 5.55)†	2.75 (1.52, 5.00)†
Low HDL cholesterol	0.03 (−0.26, 0.32)	−0.08 (−0.20, 0.04)	0.06 (−0.08, 0.20)	0.67 (0.41, 1.01)	0.94 (0.64, 1.38)
Elevated triglycerides	−0.32 (−0.60, −0.04)*	0.04 (−0.07, 0.16)	−0.04 (−0.17, 0.09)	1.01 (0.70, 1.47)	1.26 (0.88, 1.81)
Abdominal obesity	−0.38 (−0.68, −0.07)*	0.09 (−0.03, 0.21)	0.06 (−0.08, 0.20)	1.04 (0.70, 1.55)	1.12 (0.76, 1.65)

Non-LIs include cortical, large subcortical, or infratentorial infarcts. Model 1 is adjusted for age and sex. Model 2 is as model 1 but additionally adjusted for current smoking and alcohol intake, IMT, and history of cerebrovascular disease. ^aAdjusted for age and sex. ^bIncludes patients with a glucose level >6.1 and <7.0 mmol/L. **P* < 0.05; †*P* < 0.01.

adjustments for potential confounding effects of vascular risk factors had limited effects on the association between diabetes and dementia (15). Furthermore, studies in patients with type 1 diabetes, in whom macrovascular disease is generally less frequent, showed that cognitive performance is mildly impaired and global brain atrophy is more pronounced in patients with early diabetes onset (31–34).

Previous studies were mainly performed in healthy participants without or with only mild vascular disease. However, in our study population of patients with manifest arterial disease, we showed that diabetes (35) and MetS (current study) are associated with brain atrophy on top of vascular disease. It is therefore likely that other mechanisms, such as direct effects of disturbed glucose and insulin homeostasis, also play a role.

The individual components of MetS might represent some of the supposed underlying pathways and are potential targets for therapeutic intervention. Hypertension was found to be related to cerebrovascular lesions (LIs and non-LIs) in our cohort, but MetS as such was not. This can be explained by the high occurrence of hypertension in vascular patients, in both the MetS and non-MetS group. From our observed relations between hypertriglyceridemia, obesity, and brain atrophy, it seems likely that apart from glucose intolerance and hypertension, other factors can lead to brain atrophy. An elevated fasting triglyceride concentration can represent, when waist circumference is increased, a clinical marker of excess

visceral/ectopic fat. This is sometimes referred to as the hypertriglyceridemic waist. Intra-abdominal (or visceral) adiposity can induce insulin resistance through increased release of free fatty acids, production of inflammatory cytokines (adipocytokines), or reduced production of adiponectin (16,17). These metabolic and inflammatory disturbances can predispose to type 2 diabetes and atherosclerotic disease but may also directly influence the brain (36). More research will be needed to explore the precise role of these factors in brain aging.

In a previous study from our study group (3), MetS was found to be associated with an increased risk of memory and visuospatial dysfunction in patients with atherosclerotic disease. The risk of MetS on cognitive dysfunction was not greater than that of the sum of its individual components. These findings suggest that clinicians would be better off addressing the individual risk factors rather than “treating the syndrome.” Because different risk factors were associated with brain atrophy than with cerebrovascular MRI lesions, the same conclusion may be drawn in the current study.

Low HDL cholesterol significantly contributed to memory dysfunction (3). In the current study, low HDL cholesterol was not associated with brain atrophy or cerebrovascular MRI lesions. We cannot fully explain this finding, but it has been described that high HDL levels may protect against hippocampal atrophy in older people (37) and prevents inflammation (38) as well as the aggregation and polymerization of β -amyloid

protein (39). It is possible that low HDL cholesterol leads to some kind of Alzheimer-related pathology, like regional atrophy of the medial temporal lobe that we did not assess in the current study or deposition of β -amyloid that cannot be measured with conventional MRI.

Strengths of this study are the large cohort, the high prevalence of MetS in vascular patients (36.6%), and the use of quantitative MRI measurements. Our study was performed in patients with manifest arterial disease, and the lack of a nonatherosclerotic disease control group may limit the generalizability of the results. However, it should be noted that MetS is highly prevalent in such a population, and screening for MetS might thus identify those with even higher risk for structural brain changes and cognitive decline. Different definitions and different cutoff values for MetS exist, and it is yet unknown whether these same cutoff values still are valid in a study population of vascular patients. Patients with vascular disease are more frequent users of antihypertensive, glucose-lowering, or lipid-lowering medication, and not all these factors are incorporated in the ATP III criteria, and this could potentially affect the relation with outcome measures. We did not use data on lifestyle factors like diet and physical activity, which are essential treatments for MetS. It has been described that vascular risk factors may change over time. Cross-sectional studies do not provide insight into these changes and may therefore confound the association of these factors with outcome measures.

From a cross-sectional design, we can also not conclude that MetS, hypertriglyceridemia, and obesity are risk factors for accelerated brain atrophy and cognitive decline, and longitudinal studies will be needed to confirm this.

In conclusion, the presence of MetS in patients with manifest arterial disease is associated with a decrease in total brain volume of 0.72%. As previous studies report decreases of 0.18–0.23% per year older in the same age group (23–25), our findings suggest an accelerated cognitive aging in patients with MetS.

Screening for MetS and, in particular, its individual factors in patients with atherosclerotic disease may identify patients at higher risk for accelerated cognitive aging. Future studies should find out whether screening for MetS and treatment of its individual factors, in particular, obesity and hypertriglyceridemia, will prevent further progression of cognitive aging in patients with already manifest arterial disease.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.M.T. wrote the manuscript and contributed to the conception and design of the study and the acquisition, analysis, and interpretation of the data. Y.v.d.G. contributed to the conception and design of the study and acquisition of the data and critically reviewed/edited the manuscript. W.P.T.M.M. and M.M. contributed to the conception and design of the study and critically reviewed/edited the manuscript. K.V. contributed to the data acquisition and critically reviewed/edited the manuscript. M.I.G. contributed to the conception and design of the study and the acquisition, analysis, and interpretation of the data and critically reviewed/edited the manuscript. All authors approved the final version of the manuscript. A.M.T., Y.v.d.G., and M.I.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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